There is different CIN3 and cervical cancer prevalence across some of the populations. There's the use of unscreened populations at at least two of the sites, and one study was longitudinal, which was converted by the applicant to a cross-sectional study where assumptions were made that if a woman was negative at baseline -- I'm sorry -- if a woman became diseased within three years of the baseline, that she was considered to be diseased at baseline; that if she was still non-diseased at ten years past baseline, she was considered to be nondiseased at baseline.

We have an issue that perhaps not all women with normal PAP smear results were exceeded to colposcopy (phonetic). In other words, we don't have a uniform approach to account for verification bias, and as stated previously by Digene, there were two sites that did try to or did take a percentage of the negative HPV double negative patients on to colposcopy.

But then we have two other sites that perhaps cloud the issue where these sites had a self collection arm attached to it, and that women that were HPV positive and PAP negative would be going on colposcopy.

But for the self-collection part, if the woman was positive for self-collected specimen and negative with a professional collected. She was sent on to colposcopy, but the result that was reported to us in the database was the negative result for the professionally collected sample.

Now, perhaps the patient follow-up was not consistent with U.S. practice. We don't have times on when follow-up colposcopy or other treatments had taken place.

The study populations were not stratified for low risk women, and all of the studies applied to all women greater than or equal to 30 years of age.

We did have device related issues. Whereas one study was not conducted with the current Digene HPV DNA device, it was conducted with an earlier version, a less sensitive version of the Digene device.

There were unapproved HPV DNA collection devices used by three studies, unapproved in the point that we do not have performance characteristics on those devices for collection of HPV DNA for use in the Digene hybrid capture assay.

Another issue we have is perhaps there were differences in cytology readings between the

studies.

It's already been mentioned what Digene's currently approved indications are for. Since we do have these current approved indications for ASCUS, low SIL and high SIL, we evaluated the data looking at women with normal PAP smears only. We essentially have picked CIN3 as a primary cutoff because we considered that CIN3 would be less likely to regress.

There were study populations concerns. This table shows you the various study sites, the eight study sites. Footnote sites have -- the studies or partial of the studies have been published in the literature. We have the specimen type used for each of the studies. We have the lavage sample being used at Portland's cervicovaginal lavage, an unapproved brush from China, and an unapproved brush from Baltimore.

The middle column is the H range for each study site. We can see that the China study only took women 35 to 45 years of age.

The last column shows you the variation in how well the women were cytologically screened, and we're going all the way from an unscreened population to a well screened population.

This graph gives you an idea of the

overall age distribution among the sites. Only four sites are presented on this graph. The orange line is census 2000 data for women within those age groups, and we can see from the four studies listed here that perhaps it has been skewed down towards the younger age group of the 39 to 44 year.

The other four sites tended to match the census 2000 data much better.

Okay. For high risk HPV prevalence for a study site, this is some information that was furnished to us by Digene. It's been normalized by using the percentage at each site.

The yellow or gold bars are 95 percent confidence intervals for each study, and we can see that for the first six they tend to -- perhaps we'd be able to say that they have a similar HPV high risk prevalence across the sites because the 95 percent confidence intervals appear to overlap.

And in our last two studies, there is a much higher prevalence of high risk HPV at those studies.

This map gives us the CIN3 rates per 100,000 for each study. Again, this is from information that was furnished to the FDA by Digene. Again, the yellow bars are 95 percent confidence

intervals for each study.

We can see that the first four sites tend to be similar in that the 95 percent confidence intervals overlap nicely. The last four sites appear to have a much higher rate -- it's CIN3 -- than the previous four sites.

For cervical cancer, this is from information presented to us by Digene. This is per 100,000 population. The gold bar is or the orange line -- I'm sorry -- is an overall rate that was obtained from the National Cancer Institute surveillance epidemiology and end results database of 1998. The dotted gold lines are the 95 percent confidence intervals for that line.

Then we see for our first studies it doesn't seem to be approaching the overall cancer rate reported in the United States, but for our middle two, Costa Rica and Mexico, we're getting closer, but then for China, South Africa, we're much above the reported cancer incidence rate for the United States.

For device related issues, we were furnished with a study from the population that did use the previous version of the hybrid capture assay with comparison study from that population where the hybrid capture -- the previous version of the hybrid

capture was compared to the current, more sensitive version.

Positive-negative overall percent agreement was established for the study. If we look at the lower bounds of the 95 percent confidence intervals, we're at 90 percent or less on all agreements, and from the preliminary data here it appears that perhaps the two assays are not comparable.

We were also furnished data by Digene for our issue with unapproved devices being collection devices being used in several studies, and this was preliminary data where they had taken an approved collection device that's been approved for Digene's use and comparing it to the unapproved collection device.

Again, positive, negative, overall agreement was calculated, and again, if we look at the lower bounds on the 95 percent confidence intervals, it appears perhaps that with the preliminary data that the two collection devices are not comparable.

And I have to apologize for this table. It appears in everyone's handout. The positive and negative columns for both the endocervical brush and cervicovaginal lavage was switched. That was my

error, but this was information submitted to us by Digene to show the comparability between the N-cervical brush and lavage. It's information that was published by Hall in 1996.

We're really unable to evaluate the data since what we're seeing here, the groups for each of the collection methods are a different group. They are from the same population, but they're different groups of women.

So, you know, therefore, we really can't evaluate the data, but in the paper, the authors conclude or Hall concludes that the method of collection of the cervical sample was found to be variable for HPV detection. The samples collected with an endocervical brush were more likely to detect cervical HPV infections.

This is essentially my wrap-up table. We have all of the various studies listed in the first column, and there is selection bias and Xes where FDA has probable issues with the studies as presented to us for Digene's indication for use claim.

For selection bias, the information presented shows that there may have been a bias in the selection of the study groups. Some study selected participants based on no previous neoplasias within a

period of time prior to the study.

Some study populations were selected for having a high incidence of cervical cancer. In a few studies, the populations appear to be skewed towards the younger age than what's -- towards a younger age.

We have previously unscreened populations. HIV infection was an exclusion factor for all of the studies except for South Africa. So, therefore, the only HIV infected population that we know of is the South Africa population.

The spectrum bias that we have in some studies show the lower cervical cancer rate than reported for the United States. Other studies had a high risk prevalence than at U.S. and European study sites.

Two of the studies had a cervical cancer incidence higher than the U.S. average, and other studies showed a higher CIN3 rate than the U.S. and European study sites.

For device bias, this is the issue, the cervical vaginal lavage specimen, and the use of approved HPV collection devices, again, for which we don't have adequate performance established with Digene's hybrid capture assay, and also testing with a less sensitive hybrid capture assay among the study

sites.

For cytology reading, there's the issue that at least two of the sites at the cytology readings were converted to the Bethesda system from European nomenclature, and that at least one of the studies, we have the initial cytology being reevaluated with an automated screener and another study site was done by a second cytologist.

And now Dr. Kondratovich will present the statistical review.

DR. KONDRATOVICH: Good morning. My name is Marina Kondratovich. I am statistician from Division of Biostatistics.

Today in my presentation I am going to consider the following points: scheme of estimation; tradeoff between sensitivity increase and specificity decrease; and number of false positives dropping, one true positive.

Portland study, Mexican, South African study, Joman (phonetic) study, and the problem of verification bias and adjustment by multiple amputation techniques through Baysian approach.

United Kingdom and Costa Rica studies, overall information about increase of sensitivity, decrease of specificity; percent of decrease of false

negative rate. Sponsor give this name relative difference of sensitivity or another name you saw, relative sensitivity. I will use term "decrease of false negative rate."

China, Baltimore studies, and summary.

Scheme of calculation. Consider that in some studies that are in women and for every woman, she has results of two tests, HPV and PAP test. So all of these end women will be divided into four groups, A, B, C, and D. Like, for example, Group A, this will be the women with HPV positive and PAP positive. B, PAP positive, HPV negative, and so on.

Here PAP (unintelligible).

We considered the combination of HPV and PAP. It means that this combination is positive. When at least one, that is positive. So this combination A, B and C gives us results positive.

To estimate sensitivity and specificity specifically, we have to know these studies for every woman. It means the women from Group A, there are A-1 subjects with CIN3, plus disease, and A-2 subjects without disease. A-1 plus A-2 equal A.

The same for Group B and so on. The overall number n equals the number of disease subject and number of non-disease subjects.

Then from this table, we can evaluate the sensitivities of the test. Sensitivity of the PAP test will be A-1 plus B-1 divided by the total number of disease subject, N-1. Sensitivity of combination PAP and/or HPV will be A-1 plus B-1 plus C-1 divided by the total number.

So the difference in pre-CIN sensitivity will be C-1 divided N-1.

This suggested to consider percent of decrease in false negative rate. This is the percent of diseased women with normal PAP results which are detected by HPV. So it will be the ratio C-1 divided by C-1 plus D-1.

It is interesting that all combinations of PAP and/or HPV has larger sensitivity.

From this table we can evaluate specificities of this test. Specificity of PAP test alone is C-2 plus D-2 because all these women are true negative by PAP test. So specificity of PAP test alone will be C-2 plus D-2 divided by total number of non-diseased subjects.

The combination of PAP and/or HPV is negative only when both tests are negative. So the specificity of combination will be only D-2 divided by this number, and difference will be always negative.

It means that all of the combinations, combination of two tests give us less specific tests.

Prevalence will be N-1 divided by total number. Very often the women with PAP negative and HPV negative don't have verified disease study. So very often these numbers D-1 and D-2 are unknown numbers. And this problem with known like problem of verification bias.

If we put zero instead of true number, D1, then we decrease the total number of disease subjects, and then the difference between these two sensitivities will be underestimated. This difference will be too optimistic.

The same for the percent of decrease in false negative rate because you see that this characteristic depends on D-1. So if, for example, we can put artificially D-1 zero, we can get the percent of decrease 100 percent.

Verification bias can affect the estimate of sensitivity, specificity and prevalence. Estimate of sensitivity, there tends to be overestimated and prevalence tends to be under estimated.

It is easier to make conclusion about two tests, which test is better, if we have situation where one test has better sensitivity and better

specificity, but here we have situation when combination of these two tests, all have increased sensitivity and decrease of specificity.

So the tradeoff between the increase of sensitivity and decrease of specificity between PAP alone and the combination of PAP and/or HPV is very important.

The sponsor considered that 25 percent relative increase in sensitivity was being significant, but this characteristic is C-1 divided by C-1 plus B-1. It means that if this is the point estimate of percent of decrease in false negative rate, this is the 95 confidence interval. It means that lower limit of 95 confidence interval must be larger than 25 percent.

The sponsor considered that ten percent decrease in specificity was clinically acceptable. It means that if this is the point estimate of difference in specificity, this is 95 percent confidence interval. Then lower limit of this confidence interval should be larger than minus ten percent.

In reality, it's very difficult to establish one set of such numbers like 25 percent or ten percent for every study before the tradeoff between the increase of sensitivity and decrease of

specificity between PAP alone and the combination of PAP and HPV depend on the prevalence of disease.

One percent of decrease of specificity in the populations with different prevalence means different numbers of women which are false positive. So the problem characteristic like the number of false positives dropping (phonetic) true positives can be very useful.

Set for PAP alone, this is the number of false positives, A-2 plus B-2. This is the number of true positives. So if we consider this ratio, we will know how the number of false positives dropped in weren't true positives. For the combination PAP and/or HPV, this is the number of false positives, and this is the number of true positives.

Also, it's very important characteristic like for PAP negative and HPV positive. This is the amount of true positive, and this is the amount of false positive.

Then before all of these, all these women were false -- were true negative by PAP test, but after we apply HPV test, this amount of women became false positive.

This characteristic has a very useful characteristic. First, this characteristic depends --

this characteristic already has information about the prevalence.

And second, this characteristic does not depend on the verification because as you can see in this form, there is no this number D-1 or D-2 or these numbers.

Portland study. In this study the algorithm for verification of disease status was the following. The disease status of women with PAP results (unintelligible) was verified. So all women with normal PAP smear do not have their verified disease status.

HPV result was not considered in decisions of referral to colposcopy. The assumptions that those who are disease positive within three years were presumed positive at baseline, and those who are disease negative at three years were assumed to have been disease negative at baseline.

So for statistical analysis, the sponsor used the following data. For PAP negative, it was CIN3, 28 objects, subjects, and among these 28 women, 17 had HPV positive. It means that HPV has detected this women.

Eleven women were not detected by HPV. These women were false positives, 738.

So important studies, the sensitivity of PAP test was 51.7 percent. Sensitivity of condemnation (phonetic) was 51 -- excuse me -- 81 percent. Difference was 29.3 percent, and a lower limit of 95 percent confidence interval are calculated using bootstrap (phonetic) technique was 19 percent.

Specificity was decreased by minus 7.4 percent, and so the limit of this 95 percent confidence interval was minus 7.9 percent.

The percent of decrease of false negative rate here was 60.7 percent, 17 divided by 28, and lower limit of 95 confidence interval was 41, 47 percent. I calculated this by bootstrap.

Mexico study. In the Mexico study, the patients were recommended to colposcopy for any of the following: cytology abnormality, ASCUS and above; positive HPV on clinician update sample; positive for HPV on self-collected sample.

In this study, there were 5,639 women with normal PAP results and negative HPV on clinician obtained sample. Among them, 245 women, about ten percent, had colposcopy because of positive HPV on self-collected sample. So this sample was not random sampled, and among these women, two women were with CIN3+.

The sponsor considered that all other 5,394 women were without CIN3. It is too strong a conclusion. Sensitivities will tend to be overestimated.

So here all of the subjects which are PAP negative and HPV negative. Two hundred forty-five subjects had colposcopies, and two subjects had disease CIN3+. All other subjects, 243 are without disease.

The sponsor considered that all these subjects are from this group. It means that the sponsor's estimation of increase in sensitivity and percent of decrease in false negative rate were too optimistic.

We can make only assumption that, for example, that among these subjects, the probability of CIN3 is the same, like 0.8 percent. It means that 43 subjects among the subjects can be with CIN3, and then we should PAP to this 43 subjects. Here it will be total number 120, and then 30 divided by 120 will be much smaller number than if I divide 30 by 77.

Of course, this estimate will be some kind of conservative because this is not random sample. This is directed sample. These women had colposcopy result before HPV self-collected was positive, and

these women with self-collected tests are negative results, but we don't have information about performance of tests. Excuse me. We don't have any information about the probability of disease CIN3 above the subjects.

So the more correct adjustment for this bias is problematic.

(Unintelligible) study. In this study the patients were referred to colposcopy for any of the following: cytology (unintelligible) LSIL+; positive HPV on clinician obtained sample, positive HPV on self-collected sample; and two additional tests positive cervical graphics (phonetic) and evidence of disease upon direct physical examination using cervical application of five percent acetic acid.

In this study, there were 2,160 women with normal PAP results and negative HPV on clinician obtained sample. Among them, 575 women, about 27 percent, have colposcopy because of positive HPV on self-collected sample or other reasons. So this sample was not random sample.

Among these women, eight women were with CIN3+. The sponsor considered that all other 1,585 women were without CIN3. So it is too strong conclusion and sensitivities will tend to be

overestimated.

So in Africa study we have that all of these subjects are PAP negative, HPV negative. Five hundred seventy-five subjects had colposcopy, and so eight subjects had CIN3+.

All other subjects go to the self because they're without CIN3, but sponsor make assumption that among these subjects, there is no (unintelligible) CIN3. So they put all of the subjects to this category.

So their evaluation of increased sensitivity is too optimistic because if we consider that among these subjects the probability of disease, like among these subjects, then it means that this subject can have 22 additional with CIN3, and here it will be 30 subjects which are not protected by PAP and not protected by HPV.

But, again, this is directed sample. It means that this woman had positive HPV on self-collected sample or other reason, and these are different population from this.

So true adjustment for this bias is problematic. So one estimate of increase in sensitivity is too optimistic, and this may be some kind of conservative.

German study. In this study the verification of disease status was the following: that cytologic abnormality of ASCUS (unintelligible); positive AC-II HPV test and it was planned that every woman with PAP negative, HPV negative will be referred to colposcopy.

In this study there were 7,193 women with normal PAP results and negative HPV. Among them are 160 women, 2.2 percent, have colposcopy, and among them there is no (unintelligible) CIN3+.

So the sponsor considered that all other 7,033 women were without CIN3, but it is too strong a conclusion, and sensitivities are overestimated.

For statistical analysis, the sponsors used data that there are 27 subjects with CIN3+. PAP, HPV, and additionally detected 13 subjects, and HPV additionally created false positive rate or false positive number, 260.

So but here you see zero. So, for example, the percent of decrease in false negative rate will be artificially zero.

So we have that problem like there are 7,193 subjects with PAP negative and HPV negative, and we observed only that 160 subjects, and among them there is no CIN3. Can we make conclusion that all of

these subjects are without CIN3?

The disease status of these 7,033 subjects can be considered submitting data problem, and I used the adjustment for verification by multiple imputation technique through Baysian approach.

In this approach you should specify a model for the prior distribution of probability or CIN3 among subjects with normal PAP and negative for HPV. Then you should obtain posterior (phonetic) distribution of this probability on the observed data. Here is 160 subjects and zero CIN3+.

Then make multiple simulation of the disease pattern of 7,033 subjects according to the random draws from the posterior distribution.

For Baysian approach, I used sat pry (phonetic) information. That is this study the probability of CIN3 among PAP positive and HPV positive subjects were 13 divided by 43, about 30 percent. Probability of CIN3 among PAP positive and HPV negative subjects were one divided by 83, 1.2 percent. Probability CIN3 among PAP negative, HPV positive was 4.8 percent.

So I make a favorable assumption that probability of CIN3 among PAP negative and HPV negative is less than one of these three groups. So

it's less than 1.2 percent.

So I took this prior distribution, which are concentrated on this interval from zero to 142 percent with the increase in frequency now to zero. This distribution has this mean.

Then we contracted the posterior distribution that we obtained from 160 observations, and among these observations there are zero CIN3+. So this is the posterior distribution, and this is the mean of this posterior distribution.

So this mean is that the average probability of CIN3 among PAP negative, HPV negative subjects, if we observed that 150 subjects were within CIN3, it means that among 7,033 subjects PAP negative, HPV negative in average 30 subjects can be run with CIN3+.

Now let's compare these two pictures. So in sponsor presentation you sat set numbers, like there are 27 subjects with CIN3, and the HPV detected additionally 13 subjects. Sensitivity of PAP test in this situation is 51.9 percent, and sensitivity of combination PAP and/or HPV is 100 percent before it can be measured, detected. All subjects, here is zero.

Increase of sensitivity is 48.1 percent,

and percent of decrease of false negative rate is 100 percent of code because here the sponsor put zero, 13 divided by total 13, 100 percent.

Adjustment for verification bias gives us the following picture, that here it can be certain subjects because this total number women with PAP negative and HPV negative is very big number. So among them can be 13 subjects which are PAP negative, HPV negative, but with CIN3+.

So the total number of all disease subjects will be 40. Then sensitivity of PAP alone will be 35 percent. Sensitivity of PAP and/or HPV will be 57.5 percent, and like compare with 100 percent. And increase of sensitivity will be 32.5 percent.

Percent of decrease of false negative rate will be only 50 percent. Therefore, 13 divided by 26, if you compare with 100 percent in sponsor's calculation.

United Kingdom study. In this study patients were referred to colposcopy for any of the following: PAP result LSIL or worse, and ASCUS or HPV plus, that negative (phonetic).

Subjects were randomized to immediate colposcopy or all follow-up that's expected to be

retested by cytology and HPV, but this study was not completed.

In this study there were 9,291 women with normal PAP results and negative HPV. Among them are 278 women, three percent, had colposcopy, and there is not any CIN3. So the sponsor considered that all other 9,013 women were without CIN3+. So sensitivities are overestimated.

So for statistical analysis, the sponsor used the following data: that in this study it was 51 CIN3+ subjects and HPV additionally detected four. So increase of sensitivity was 7.8 percent or divided by 51, with low limit of 95 percent confidence interval. That's 1.96 percent.

Percent of decrease of false negative rate was, of course, 100 percent, four divided by four. Using the multiple imputation technique through Baysian approach, and I use this thing very favorable prior distribution, that the probability of CIN3 among HPV negative and PAP negative subjects is less than among all other three groups.

We can obtain that it can be additionally 16 subjects with CIN3+. So instead of zero, we should use there 16. Then increase of sensitivity will be six percent, with lower limit of 95 confidence

interval as 1.5 percent, and percent of decrease of false negative rate is only 20 percent, not 100 percent.

Costa Rica study. In this study patients were referred to colposcopy for any of the following: cytology abnormality, ASCUS plus; positive cervical gratia (phonetic); suspicion of cancer upon physical examination.

Among 7,176 patients, only 769 subjects had the HPV resolved by AC-II; others by AC -- HCS (unintelligible). The HPV status was not used as a criterion for referral to colposcopy. An additional 128 randomly chosen women with normal screen results, it means that these tests were normal where referred to colposcopy, and among them there is no CIN3+.

The sponsor considered that other 5,632 women with normal screen results were results CIN3+. So the sponsor's estimate of sensitivity can be biased.

The sponsor reported that the women under age 30 were likely included in this control group and that they don't have information to identify the portion of these women among 128.

Also, it isn't clear how many women were with HPV positive and HPV negative among these 128

women with normal screen results.

So the information for adjustment of verification bias was absent.

This is overall table for sensitivity and specificity of PAP test alone, of PAP and/or HPV. So in (inaudible) submission you can see there like PAP, before months (phonetic) of PAP, combination PAP and/or HPV. Like Portland, 81 percent; Mexico, 97.4 percent; and South Africa, 92.5 percent; in Germany, 100 percent; the United Kingdom, 100 percent; in Costa Rica, 94.1 percent.

But if we make adjustments like in Mexico because in Mexico there are directed samples; so the four months of PAP and/or HPV will be only 62.5 percent. In South Africa, it will be only 76.7 percent, but this estimation can be conservative because these two samples are directed.

In Germany and United Kingdom we had random sample, and so we can say that this estimation is very realistic. We cannot say that they're conservative.

So in Germany, instead of 100 percent, we have 67.5 percent, and United Kingdom we have 76.1 percent. In Costa Rica, there is no information for adjustment.

I did not put information for adjust the specificity because it's very small differences, and so specificity is not so affected by verification bias as sensitivity estimated.

This is overall increase in sensitivity and decrease in specificity. So in Portland study the increase in sensitivity was 29.3 percent, with low limit of 19 percent, and decrease in specificity was minus 7.9 percent, low limit of 95 percent confidence interval.

In Mexico study, in PMA submission, in the sponsor's calculation, the increase in sensitivity was 39 percent with low limit of confidence interval, 28.6 percent. In this study the specificity was decreased minus 5.4 percent, with low limit minus six percent.

In South Africa, in PMA submission, the sensitivity increase was 8.4 percent, but with low limit of 95 confidence interval, 3.7. After adjustment for directed sample, this increase was 6.9 percent with confidence interval, a low limit of 95 confidence interval, 3.1 percent.

In this study, the decrease of specificity was -- point estimate was minus 10.1 percent and lower limit of 95 percent confidence interval for difference was minus 11.2 percent.

In Germany, in sponsor calculation there are number like increase in sensitivity of 48 percent, but after adjustment because there are random samples and after adjustment by Baysian approach, this increased only 32.5 percent, and low limit of 95 percent confidence interval, 17 percent, 17.5.

In United Kingdom, their increase of sensitivity was 7.8, and confidence interval very small, two percent. After using Baysian approach, increase on six percent with a lower limit of 95 confidence interval, 1.5 percent.

In Costa Rica studies, increase of sensitivity 16 percent and low limit of 95 confidence interval, 7.3 percent.

This is the percent of decrease in false negative rate. In Portland study, the percent of decrease of false negative rate was 60.7 percent, and this is lower limit of 95 percent confidence interval. I calculated this confidence interval using bootstrap technique.

In Mexico study, in PMA submission you can see that the percent of decrease from false negative rate, 93.8 percent, but this is too optimistic evaluation, and if we used directed samples, then percent of decrease of false negative rate is only 40

percent, and lower limit of 95 confidence interval is 28.6 percent, more than 25 percent.

South Africa, in PMA submission it was 52.9 percent, but if we use directed sample, we have only 23.1 percent, and lower limit of 95 percent confidence interval is 10.5 percent. So it's less than 25 percent, and this confidence interval is more than 25 percent. So maybe realistic estimation will be somebody between these two numbers.

In Germany, in PMA submission you see that percent of decrease 100 percent, but if you use random sample it's only 50 percent, and using Baysian approach, and lower limit of 95 percent confidence interval is 34.4 percent, is larger than 25 percent.

The United Kingdom, you see that the percent of decrease of false negative rate, 100 percent, but after using Baysian approach is only 20 percent and very small confidence; lower limit of 95 percent confidence interval, 4.5.

In Costa Rica this data is biased, and there is no information to correct this data.

For China and Baltimore you san see 100 percent, but this is one divided by one. China is in some kind of unique because in this study there is no verification bias. All women underwent colposcopy.

And results of PAP and HPV test with disease status were foreign (phonetic). In this study, it was 42 subjects with CIN3+, and PAP test detected 41 subjects. HPV test detected only one subject additionally, but false positive rate was increased by 159 subjects.

So in these studies there are different sensitivities. There was only one divided by 42, 2.4 percent. Lower limit of 95 percent confidence interval by using bootstrap technique was zero.

So I make conclusion that this data did not demonstrate that in case of sensitivity was statistically significant, but lower limit of 95 percent (unintelligible) confidence interval of one divided by 42 is 0.0006, but if you use exact method to calculate this confidence interval, then you don't count the variability from PAP performance.

Baltimore study. In Baltimore study, patients were referred to colposcopy for any of the following: PAP result LC or worse, and PCR HPV are positive results. Women with ASCUS PAP results and negative PCR HPV were not referenced to colposcopy, and so this point excluded 57 subjects from the statistical analysis.

There was a discordant between results of

PCR and AC2 HPV test. Women with ASCUS results negative, PCR HPV test, but with positive AC2 HPV test were not referred to colposcopy, and they also were excluded from statistical analysis.

In this study there were 991 women with PAP negative and AC2 HPV negative. The 53 women with PAP negative and AC2 HPV negative, but PCR HPV positive were referred to colposcopy, and among them there is no CIN3+.

The sponsor considered that other 938 subjects were the subject without CIN3+.

In this Baltimore study, the sponsor considered the following data: that there were two subjects with CIN3+, and PAP test detected one subject, and HPV detected additionally one subject. So the difference was -- difference in sensitivities was 50 percent because PAP alone has sensitivity, 50, and combination has sensitivity 100 percent. But first, these data are very biased.

So I make conclusions that these data did not demonstrate that increase of sensitivity was statistically significant because very small sample size and also the zero is not true number, can be not true number.

So it's very important question about

tradeoff between increase in sensitivity and decrease of specificity, and obviously that this tradeoff depends on the prevalence.

The number of false positives necessary to obtain one true positive is very useful characteristic, and in this table you can see this column gives you the prevalence of CIN3, and this column gives you the ratio of false positives to true positives to the PAP negative and HPV positive.

So for the Portland study, in order to get one true positive woman, 43 women should be considered like false positive. In Mexico, this is 11. In South Africa, 32; in Germany, 20; in United Kingdom, 39; in Costa Rica, 23; in China, 159; in Baltimore, 22.

I build up the limit of 95 percent confidence interval by using bootstrap technique, and you can see that this number is -- gives that estimation, what kind of false positive number you can expect. In United Kingdom, it can be 161. In Mexico, as much as 15. In Portland, it can be as much as 69.

So this is the column on prevalence, and I would like to emphasize that this number is not affected by verification bias and have some information already about the prevalence of disease.

So my overall summary is that the concrete

numbers of increase of sensitivity different then relative difference, affected by verification bias. In (unintelligible) submission, the sponsor calculations, they increase sensitivity and percent of decrease in false negative rate were usually overestimated.

The submitted data of China and Baltimore studies did not demonstrate statistically significant increase in sensitivity when combination of PAP and HPV test was used.

There were no advanced judges (phonetic), the other biases, such as spectrum bias due to the different prevalence, bias due to different sample collection devices and others.

What tradeoff between increase of sensitivity and decrease of specificity acceptable is the clinical question.

Thank you very much.

And right now, Dr. (unintelligible) will present the question.

CHAIRMAN WILSON: I actually think we're going to defer questions at this time to the open committee discussion later this afternoon. Thank you for your presentations.

At this time we're going to move to the

open public hearing. Public attendees who have contacted the Executive Secretary prior to the meeting will address the panel and present information relevant to today's issue.

Speakers are asked to state whether or not they have any financial involvement with the manufacturers of these devices, and these presentations will be in the order that they were received by the Panel.

I'd like to remind the speakers that they have three minutes each, and they'll be interrupted if they go over. The last four presentations are statements which Ms. Poole will address.

The first presentation is by Ms. Mary Mitchell, representing ACOG.

MS. MITCHELL: Thank you for the opportunity to provide the recommendations of the American College of Obstetricians and Gynecologists on HPV testing.

I am Mary Mitchell, ACOG's Director of Clinical Practice in the areas of gynecology, primary care, and ethics. I personally have no financial involvement with Digene or Cytec. Both companies are members of our Friends of ACOG program for industry.

ACOG's recommendations on HPV testing

appear in Guidelines for Women's Health Care. This week we have released the second edition of guidelines, and these recommendations are from that edition.

First, HPV testing as a primary screen. We believe that HPV testing lacks the specificity necessary to be a useful screening test for cervical cancer or precursors because the vast majority of women with HPV DNA detected from cervical lavages would be cytologically normal.

Second, HPV testing for triage purposes. HPV testing with identification of specific HPV types may be of value in the triage of certain subsets of patients. Before it can be recommended for routine clinical use, however, we believe that its use, along with cytology, must be evaluated prospectively in a clinical trial.

Guidelines for Women's Health Care derives its recommendations from ACOG's Committee on Gynecologic Practice and other established authorities. Although the second edition has just been published, the content was finalized before last year's significant events regarding cervical cytology and HPV testing.

Thus, Guidelines does not reflect the

baseline results of the ALTS trial or the September 2001 consensus conference sponsored by the American Society for Colposcopy and Cervical Pathology.

The Committee on Gynecologic Practice is currently reevaluating ACOG's position on HPV DNA testing. Should it develop new recommendations based on these recent data, the new guidelines would be published in our Journal of Obstetrics and Gynecology.

In summary, ACOG recognizes the laboratory tests for the detection and typing of HPV infections are currently available in many parts of the country. At this time, it does not appear that such testing is clinically useful.

On behalf of ACOG, I thank you for the opportunity to provide this information, and I'm happy to answer any questions.

CHAIRMAN WILSON: Thank you.

Does anyone have any questions?

(No response.)

MS. MITCHELL: Thank you.

CHAIRMAN WILSON: Very much.

Our next presentation will be by Dr. Linda Alexander from the Women's Advocacy Perspective.

DR. ALEXANDER: Good morning. I'm Linda Alexander. I'm immediate past President of the ASHA,

the American Social Health Association, current President of Advocates for Women's Health, and I have no financial interest in Digene.

Thank you for the opportunity to provide a few statements at today's hearing. My comments today will examine the proposed application from the women's health advocacy perspective.

The data available today clearly support the value of this test in general population screening of women 30 and older. It is neither my role nor platform to debate with you the significance and clinical implications of these data. Rather, I would like to approach the discussion and decision as an opportunity to move the women's health agenda forward.

We must all applaud and acknowledge the tremendous success of our traditional cervical cancer screening and prevention efforts. Indeed, our success in cervical cancer has been the logical foundation and benchmark for many other national and international cancer screening initiative.

Yet our efforts, while laudatory and impressive, are far from perfect. It's tragic that thousands of women still die each year in the U.S. and thousands of others suffer with associated physical and emotional morbidity.

As a public health practitioner, I feel we should note that today we are afforded an opportunity to move cervical cancer screening in the U.S. into a truly primary prevention activity where we will seek to identify the causes of high risk papillomavirus.

Our traditional PAP smear, while often hailed as an example primary prevention, is, in fact, a secondary prevention modality that identifies cancer after it is manifested as a disease state.

The transition for general cancer screening from a secondary to primary modality is a major public health and women's health success story. So from a women's health advocacy perspective, it's time to admit that our standard of care in promoting traditional annual PAP testing is somewhat inadequate.

Advances in molecular diagnostics permit more than a PAP with a single examination. The combination PAP and HPV test is invaluable to clinicians and patients in determining the absence of high grade cervical cancer.

And I would submit that from an educational perspective it's time to help women understand more clearly that a normal result from traditional PAP does not equate to a clean bill of gynecological health. It's time to help women

understand that the regular gynecological exam is an opportunity not only to screen for cervical cancer cells or other high risk form of virus that causes cervical cancer, but also it's time to check for other often silent reproductive tract infections.

It's time to acknowledge that infections of the reproductive tract afflict women more often and with more adverse consequences than men. These infections are a source of considerable shame, stigma, and anxiety.

We as a society, in spite of our sexual openness, really are socially challenges to talk about STDs. It's time for improved communication for women's health care.

The new proposed standard of care, PAP plus HPV test, is a tiny first step forward to break down the communication challenge. It can help establish a new patient-provider dialogue addressing the reality that infections are rather common. Treatments are available from the host, and that the regular gynecological exam is a forum for discussion, diagnosis, and treatment.

We are grateful to our foremothers in Women's Health Advocacy for their tenacity and determination to improve women's health. We are

grateful to our mothers who began the era of women's medical education, and we are grateful to our sisters who gained momentum in reproductive rights, and we can claim success for our efforts in the new scientific agendas in gender based biology and women's health research.

But we, the women of the new century, now have new issues to promote: the advancement of improved technologies, improved education, and improved access in utilization of health care resources for all women.

Today women's health advocacy efforts continue, and we are the next major threshold in the era in women's health. Medicine and health care are technological revolutions, where molecular and genetic insights and diagnostic capacities never before possible are before us.

And we are in an information age where Internet access provides anyone the latest medical studies. Women's advocacy efforts for this century will clearly incorporate these phenomena.

Today from a women's health perspective it is as significant and important as the day that the original PAP was proposed and accepted as the standard for cervical cancer detection.

We today, the assembled team of parties with disparate interests in women's health, encourage the panel to consider the significance of this application to improve the current clinical paradigm of preventive gynecological health. It will concurrently improve the education opportunities for women in a clinical context.

Maybe, and perhaps more importantly, today affords the opportunity for women's gynecological care to move forward into new generations of technology and information that will eventually provide comprehensive diagnostic opportunities with routine examination.

Thank you very much.

CHAIRMAN WILSON: Thank you.

All right. Our next presentation will be by Ms. Phyllis Greenberger, who is the Executive Director, Society of Women's Health Research.

(No response.)

CHAIRMAN WILSON: Okay. She's not here. Then we'll hear from Mr. Wayne Shields, who is the President and CEO of the Association of Reproductive Health Professionals.

MR. SHIELDS: Hi. Thanks for the chance to come today and give you some comments.

As Dr. Wilson just stated, I'm Wayne

Shields. I'm President and CEO of the Association of Reproductive Health Professionals. I'm here and I'm speaking on behalf of our physician, nurse midwife, nurse practitioner, physician assistant, and health research members, and our board of directors.

I'm speaking from notes. I didn't get them included in your packet so I brought further copies for your reference later. So you can probably get them in the back.

ARHP, my association, is an interdisciplinary membership based association, and it's composed of professionals who provide reproductive health services or education or conduct research or influence reproductive health policy. We were founded in 1963 with a mission to educate health care professionals, public policy makers, and the general public. And we foster research and advocacy to promote reproductive health.

We're nonprofit, and we firmly abide by national accreditation guidelines for industry support established by the FDA and established by the Accreditation Council for Continuing Medical Education, the ACCME.

ARHP develops accredited educational programs and enduring educational materials for health

care providers, and we also educate the public about important reproductive health issues.

We receive support from our members, from foundations, from corporations, and from government agencies for our work.

For disclosure purposes, ARHP received an unrestricted educational grant in 1999 from Digene to produce a clinical monograph. Funding was not provided for participation today, and I have no personal interest, financial interest, in Digene.

This statement is written and presented to you to express ARHP's support for a woman's right to quality health education regarding the human papillomavirus, its relationship to cervical cancer, and the safe and effective options available for diagnosis and treatment.

We recognize the important goal of improving screening and diagnosis of HPV to reduce the unacceptably high rates of cervical cancer in the U.S., and to meet these needs, we strongly encourage all efforts to make as many safe and effective diagnostic methods available to women as possible.

It is understood that HPV is not a new emerging virus. However, almost all of our understanding of the natural history and the

epidemiology of this group of viruses has only come about in the last 20 years with the advent of sensitive molecular testing that facilitated a description of the more than 100 HPV tests that we have now identified.

We now understand that genital infections with HPV is the most commonly sexually transmitted viral infection, and that this virus manifests itself as more than just benign warts, but has the capacity for oncogenesis.

With this wealth of information as the basis for educating women and their partners, we believe at ARHP that there are sufficient data to establish the safety and effectiveness of new technologies and diagnostic options for HPV, particularly the DNA testing option under discussion today.

Approving this new option will enable women access to improved technology that can save lives, and it can do this while avoiding unnecessary procedures and visits to health care professionals and providers, and these are all important goals at ARHP. And this is a positive step for women who have the right to accurate and reliable HPV information.

CHAIRMAN WILSON: Thank you.

Ms. Poole, would you like to acknowledge the four written statements?

MS. POOLE: We have a copy of Dr. Greenberger's presentation. It's in your handout. Dr. Greenberger stated that she felt there was sufficient data to assess the effectiveness of combination screening and urges that a decision be made as quickly as possible.

The second statement we received was from Dr. Philip Miles, the Medical Director of GYN PATH Services, Incorporated. Dr. Miles believes that performance cytology in combination with HPV can significantly improve our cervical cancer screening program, especially for women over 30.

Dr. Keith Reeves from Houston, Texas, believes that within the past couple of years we have been able to expedite the diagnosis and treatment of patients who have abnormal PAP smears by using the demonstrated capability of the thin prep. PAP test, and he thinks that the HPV is an important and proven testing algorithm in saving women's lives.

We also have a statement from Dr. Elinor Christiansen, President of American Medical Women's Association. Dr. Elinor Christiansen states that AMWA supports women's access to comprehensive, accurate,

and affordable health care services, and they believe that women have a responsibility to be actively involved in their health care and supports the use of the HPV with PAP testing.

The final statement was received from Dr. Marshall Austin from Coastal Pathology Laboratories, and Dr. Austin also concludes that the increased negative predictive values of Digene's hybrid capture II HPV testing combined with liquid based thin prep. cytology offers significant improvements in sensitivity and could, with appropriate study, lead to safely lengthening of the usual screening intervals.

Thank you.

CHAIRMAN WILSON: Thank you, Ms. Poole.

Is there at this point anyone else who would like to address the Panel?

(No response.)

CHAIRMAN WILSON: Okay. If not, the open public hearing session is now closed.

At this point we'd like to break for lunch. We are behind schedule. So I'd like to reconvene the meeting promptly at 1:15 rather than one o'clock.

So 1:15. Thank you.

(Whereupon, at 12:27 p.m., the meeting was

recessed for lunch, to reconvene at 1:15 p.m., the same day.)

A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:24 p.m.)

CHAIRMAN WILSON: This part of the meeting is devoted to an open committee discussion. It is open to public observers. However, public observers may not participate except at the specific request of the Chairperson.

At this point I'd like to ask the FDA to put up the first question.

If you could read that, I'm sure not everyone can see that.

MR. SIMMS: The first question the FDA would like to propose to the Panel is: does the data submitted support use of the HPV DNA testing as a general population screening test in conjunction with PAP smear, considering the non-U.S. population study showed differences in cervical cancer prevalence and screening practices versus the U.S. population?

Three studies used collection devices with unestablished performance, and one of these an invalidated matrix. One study defined positive using any positive result up to three years after testing, and cytology readings and selection of patients for colposcopy were not standardized across studies.

CHAIRMAN WILSON: Okay. Thank you.

I'd also like to remind the Panel members at this time if they feel they need additional information from any of the speakers this morning, we can ask them to come up to the podium.

So at this point I'd like to open the meeting up to discussion from the panel members if anyone would like to start with any comments or questions.

Dr. Koutsky.

DR. KOUTSKY: I guess I thought we were voting on does the data support the use of high risk HPV testing among women 30 years of age or older as a general population screening test in conjunction with PAP smear. Is that --

CHAIRMAN WILSON: This is the time to give input to the FDA, but we won't be formally voting on this. We'll be voting on the indication later, but this is the time to answer the questions they have about the proposed intended use of the product.

DR. FELIX: So is this Question 13 with 30 and over?

CHAIRMAN WILSON: It is, yes.

DR. KOUTSKY: And it's pertaining to the high risk group.

CHAIRMAN WILSON: Go ahead.

DR. KOUTSKY: I think a lot of important information has been presented, and I would just like to address some of the issues up on the slide and some of my thoughts in reviewing the information that's been sent and listening to the presentations by both Digene and the FDA.

I think with respect to A above, I think in the U.S. we're in a sad situation where we have different screening practices for different populations, and I think it's incorrect to view the U.S. population as a homogenous population of women, and I think that, for example, we do screening in planned parenthood populations in a county south of the county Seattle is in, which has no health care system, and we have rates of CIN3 that are higher than what were reported for the China study.

So I think that there, on one hand, there's a real advantage to having a diversity of studies. I think also there is an advantage to having studies that are not solely sponsored by the company, that are conducted by a variety of different investigators.

I think also this is a collection of studies using different procedures, different strategies for identifying women for PAP smears that

were not uniformly read.

Again, in thinking about the advantages and disadvantages, another advantage is that as we've heard today and in other venues, cytology is poorly standardized, and I think there's an advantage to seeing under a variety of different conditions, a variety of different clinical settings the performance of the hybrid capture II and to be able to evaluate in a variety of different settings.

The issue around the device, to my knowledge, the unapproved devices are less sensitive than the approved device, which would actually only sort of tend to bias the results to suggest sensitivity was less than what it would actually be if a more sensitive test was used, and that may, indeed, suggest -- I just -- I haven't -- to my way of thinking, the device issue seems to be less problematic compared to the fact that performance should only improve with a recommended device.

CHAIRMAN WILSON: Dr. Berry.

DR. BERRY: Dr. Wilson, I wonder if I can show in a slide some of the statistical things from this morning that I think in a single slide addresses --

(Laughter.)

DR. BERRY: -- addresses the issues from my perspective, and I don't know how to answer this question without asking something on that slide. Can I show that?

CHAIRMAN WILSON: By all means, go ahead.

DR. BERRY: Greg, I wonder if you could find -- could you do that thing?

DR. FELIX: Could I ask a question while doing that?

CHAIRMAN WILSON: Sure, go ahead, Dr. Felix.

PARTICIPANT: Excuse me. Do you have it loaded onto the computer?

DR. BERRY: It is. He knows where it is.

DR. FELIX: While they're trying to find that, I wanted to ask regarding the devices, we've sort of skirted the issue, but is this panel considering HPV testing out of the liquid medium? This preserves it as approved or not?

I think it has FDA approval.

DR. GUTMAN: Yes, yes.

DR. FELIX: Okay. Because I think that in one of the studies, FDA analysis said that the Costa Rica study was not an approved device, but I think they did those out of the preserves it.

CHAIRMAN WILSON: We can ask FDA to address that.

DR. GUTMAN: It's related to the collection device, not to the process and material. The sampling device.

DR. FELIX: The sampling device?

DR. GUTMAN: Not the liquid base.

DR. FELIX: And it's -- okay. Because I thought that the sampling device out of the liquid base meaning it could be either the spatula and brush or the broom device.

DR. GUTMAN: They were both approved for the PAP smear, but not approved for use by Digene.

DR. FELIX: Thank you.

CHAIRMAN WILSON: Dr. Berry.

DR. BERRY: We do tests not because they're sensitive. We do tests because we're going to change the way we behave depending on the results of the test.

So sensitivity to me is important in doing the right calculations, but this business of 25 and ten, I think, is irrelevant.

This is what I think is relevant. The most important question is what happens if the PAP test is negative and the HPV test is positive, and so

what I have here is the process over time with respect to the eight studies.

I've taken the liberty -- see, I can do that -- I've taken the liberty of actually adding up the numbers. We're told by the FDA and the sponsor that these are not poolable, but we have to make a decision to recommend approving the device. We're not going to recommend approving it in Portland and not in Baltimore.

There's heterogeneity in the study obviously, and that's an advantage, and the appropriate way of pooling, I think, was intimated earlier by the sponsor in Baysian hierarchical analysis. I haven't done that. I've just added them up.

So anyway, the total is at the bottom. The first column of numbers is the prevalence of the disease in the various studies. This is subject to verification bias, of course. The first two columns of numbers are subject to verification bias. The third one is not.

The proportions varied, and this was Dr. Koutsky's point. The proportions varied from very small to very large. On the average there was about one percent disease.

After you get a negative PAP, that drops considerably as you see. Just by way of reference, the first number for Portland you remember a sensitivity of 50 percent. The negative predictive value, therefore, drops by about a half to .028, as you see. On the average it drops by about a factor of 25 percent or so.

Now, what does the HPV test add? The HPV test, if it's negative, as we know, drops precipitously. If it's positive, and this is the issue, if it's positive, the numbers come back up.

This third column is really what Dr. Condrot -- Marina --

(Laughter.)

DR. BERRY: -- talked about when she said the number of false positives to get one true positive. This is the ratio of the true positives to the total number of positives, and you see -- and this is a critical issue now -- what do we do when that happens?

If we do exactly the same thing as if the HPV test were negative, then the test has no value. I've heard people suggest that if it's positive then we might retest, call the women back after 12 months or maybe even sooner.

If, on the other hand, it's negative, then we might go for three years. I mean, the issue to me is what are we going to tell women if this happens. What are we going to tell physicians? Are we going to -- and I think it's essential for the sponsor and the FDA to come up with some guidance for physicians and for women should this happen, and it had better be the case that the guidance is different depending on whether you get a negative or a positive screen.

You see that overall it increases to above the prior value, which I think is important. It means that someone who is negative and then positive on HPV has higher risk than in the general population, and therefore, something ought to be done.

The only two studies where that's not the case is South Africa and China, but generally it increases to about four times what the prior value was.

I think that's important, but what I want to hear is what impact it will have. Will it, in fact, mean that the screening interval will be shorter? Will it mean that the rate of colposcopy will be greater?

And if so, then I think my answer is yes to question one.

Just a couple of other points while I'm talking statistics. The issue of borrowing strength with respect to verification bias, I mean, verification bias is important for sensitivity. It's less important for these calculations that I've shown here.

I do think that the borrowing strength that's suggested by the company is a reasonable one.

The issue, Killackey said women are smart, and I completely agree with that. I've used that phrase at least 100 times in the past month in a different context.

(Laughter.)

DR. BERRY: And what we've got to do is convey uncertainty to women, and I think we can do that.

The business about the gray zone, I do think -- I mean, the right-hand column depends on a positive HPV. If it's positive or just barely positive, as opposed to negative but just barely negative, those two numbers would be quite similar, and I do think that if we are focusing on certainty, that the gray zone, the actual quantification of the viral load would be important.

So my bottom line, Dr. Wilson, is I need

to know what the implications of a negative and then a positive HPV would be before I can vote.

CHAIRMAN WILSON: Any members of the panel care to comment on what those implications would be?

Dr. Noller.

DR. NOLLER: I think I'm the only gynecologist on the panel, so the only person who maybe sees a lot of these women.

Women who have a positive PAP smear think they have cancer, and we spend a lot of time convincing them that it's a screening test and they need further evaluation. There's anxiety. There's nervousness that's appropriate, and we spend a lot of time talking to them about what a PAP really means.

Another test on top of that that's positive, whether the PAP is positive or negative, will also increase their anxiety. All of that will translate into more colposcopic examinations, and with those examinations more disease will be found.

More disease would be found though if the PAP smear were repeated in a year and HPV testing wasn't done. Virtually anything you do besides the PAP smear increases your pick-up of cases, if you will.

If you reread the same PAP smear on a

slide twice, you're going to increase the pick-up. So it's hard to -- I mean, you're going to pick up more disease no matter what you have, but this definitely will increase the number of colposcopies, and as the analysis from FDA showed, we'll have to do quite a few colposcopies to pick up one case of real disease.

I think it's difficult to know where you should put that bar, one in ten, one in 20, one in 1,000. It's very difficult, but this will increase more colposcopies and biopsies, most of which will be done in women without disease.

DR. BERRY: And how about interval? Will it change the interval?

DR. NOLLER: It's very difficult to know. The annual PAP smear, in quotes, has been part of the practice of gynecology since the mid-'60s. It's kind of unclear why annual PAP smears were -- why the annual smear instead of biannual or triennial.

Probably it has more to do with the fact that in the '60s the birth control pill was approved, and women had to get a PAP smear to get their birth control pills refilled, and the annual smear became sort of fixed at an annual smear.

And of course, there's a whole body of data about what happens if you go from annual to

biannual to triennial.

Will it change? I think it will take a long time. The changes from always an annual smear to the recommendations that sometimes you can extend the interval have not extended it for a lot of women. Many physicians, many patients still expect that they have a PAP smear every year, regardless of the fact that they might have had 15 negative smears and are traditional low risk and really don't need another one.

CHAIRMAN WILSON: Dr. Felix.

DR. FELIX: I'd like to make a comment. I agree with you, Dr. Noller, that a lot of the physician-patient relationship in gynecology is based on the annual PAP, and those are trends that are very difficult to break. So, in fact, if there was an extension of screening which I inquired earlier about, it would have to involve a great deal of education to the gynecologist and to the patients.

The possible exception to that, and it's a growing trend in the United States, is managed care, and managed care, I think, the statistics are that a significant proportion of the population are in managed care currently, and if the recommendations from a managed care institution is that after a

negative test the patient's screening interval is expanded, then that may be a group, a very significant group of women, where that will be instituted.

So that's the one caveat where that may occur very quickly because of the access to their health care.

CHAIRMAN WILSON: Dr. Beavis.

DR. BEAVIS: Thank you.

The whole comment, multiple comments that have been made about expanding the interval, are very appealing intuitively. The problem that I have with that though is that I don't feel that we have been presented with data to support that.

If we say that that's the hypothesis, that it could be used to extend the deadline, to expand the screening interval, the data would probably support that, but I would argue that we just don't have that here.

And my concern is the concern that Dr. Noller expressed, which is that it could possibly lead to increased colposcopies.

CHAIRMAN WILSON: Dr. Reller.

DR. RELLER: I look at the studies that we've been presented more in the category of hypothesis generating, along with Dr. Felix's comment

and those made just prior to it, that one could increase or decrease the interval for different populations based on this test is plausible, but not proved.

I mean none of the studies was designed to answer that question, and I think that's the reality of what we have.

It could be done, but we don't have the data. I mean, the studies could be performed to validate the concept that one could increase the interval or decrease the interval. We just don't have those data.

CHAIRMAN WILSON: Dr. Durack.

DR. DURACK: Just to extend the last two comments, I also have some concern about this area. On the one hand, we have had several hints that this is an obvious benefit of the application, that we would extend the interval, and I think it's been mentioned several times, and clearly there are some potential benefits for that.

On the other hand, as we just heard, the data don't necessarily support it. We also heard in the presentations we're not actually recommending that. So we've got a little tension here between here's something good, and we're not actually

recommending it.

So I think we have to be very careful with this issue. There may also be unintended consequences, of course, which is less frequent visits. You don't notice something else, whatever it might be. The possibility of the unintended consequences of an extension which require further investigation.

So I guess I'm saying that perhaps this should be put to one side in answering the question, if it's possible to do that, the whole issue of extending the interval.

CHAIRMAN WILSON: Good point.

Would anyone from Digene care to comment about the issue of what the impact is of a -- as Dr. Berry described it there for a PAP negative but HPV positive test?

DR. KINNEY: As you've heard earlier, the current standards around the country are for PAP smear screening somewhere between one and three year intervals. There is no suggestion that we want to extend the intervals past what is currently accepted clinical practice.

And in fact, if three years is considered an extension, that's already happened. What we'd like

to do is to be able to practice more safety within the confines of what is currently accepted clinical practice, and if given the tools to be able to do that, then we'll do it.

DR. COX: I have nothing to add to that. That's what we've been saying all morning, is that clinicians have not taken advantage of the intervals that have been offered in present PAP screen guidelines because of obviously concerns. I believe that we can diminish that concern and allow that to be utilized at the discretion of the clinician.

CHAIRMAN WILSON: Dr. Reller.

DR. RELLER: A little more?

DR. KILLACKEY: I would just add and reiterate, when we do get this and they do understand this, women now know that there is a recommendation to be screened every three years. They hear it from their health insurance companies.

For example, there's a tremendous amount of pressure. I constantly fight for patients to sometimes get more frequent PAP smears when it's indicated.

Women do understand, and if you just explain to them that if you are PAP negative and HPV negative, you are now a low risk woman. Nothing is

going to happen to you for the next two or three years. It's really okay to get PAP again in three years.

We are not changing or extending guidelines.

DR. KINNEY: The other point that warrants mention is that Dr. Noller makes mention of the increased colposcopy. The only circumstance under which we're suggesting that should occur is if somebody has a positive cytology on a subsequent examination.

CHAIRMAN WILSON: Dr. Reller.

DR. RELLER: So if I understand correctly, based on the positive HPV HC2, you're not going to do anything. You're only going to act if you have something else, and you're going to stay within the boundaries of current guidelines based on risk, multiple aspects thereof.

Now, how exactly is this test a positive to be used to say it should be one year or three years or something in between that? And where are the data to support that change within the current boundaries?

I mean, where are the studies that show that you can safely, effectively do that where the benefits outweigh the potential risks that have been

mentioned?

I mean within the one to three. I mean not --

DR. KINNEY: Dr. Bosch, when he was speaking this morning, put up a slide that demonstrated five different studies with negative cytology and positive HPV that showed that the relative risk of subsequent development of high grade dysplasia was on the order of ten to 20.

We've had that same experience with our own cohort in our Portland group, and as a consequence, we feel that that's reasonable to do.

The Kaiser Portland cohort, as you're aware, is the longitudinal undertaking. I mean, it seems to me there's a big difference between being plausible and being proved with a clinical trial.

DR. RELLER: Obviously each observer's threshold of belief is different, but we believe that our understanding of cervical carcinogenesis and of the dramatically elevated risks of subsequent dysplasia associated with carriage of HPV warrant that.

DR. COX: I would have to say that although it wasn't put in the data submission here, there are multiple longitudinal studies that do show

that individuals remaining persistently HPV negative are at no risk of development of CIN3, and in fact, one study out of Holland shows that individuals that are only intermittently HPV positive have no risk of subsequent development of CIN3.

DR. FELIX: And those are using HC2, Tom?

CHAIRMAN WILSON: Dr. Birdsong, then Dr. Beavis.

DR. BIRDSONG: I'm concerned that there's -- although Dr. Cox addressed the issue of follow-up with a PAP negative, HPV positive woman this morning, you know, you stated that that was basically your personal preference, and that makes sense to me, too, but as the first comment indicated, I think, you know, despite what you said, you know, in the absence of or even if there was a specific recommendation to do something like that from the company, I think also there probably will be a lot more colposcopies because even if the, you know, clinician doesn't think they're necessary because they think there will be a tremendous amount of stress and anxiety produced by the knowledge of a woman knowing that she's HPV positive with a known increased risk, you know, in addition to whatever social stigma there might be.

And I agree with the earlier assertion

that education is a very important part of it, and I'm a pathologist, but still you know, based on the conversations with the gynecologists I work with, and that's with a high risk population, I think that they will still come under a great deal of pressure to do something other than, you know, wait a year to take another look.

And you know, this is -- I don't think this is without consequence because I think even despite the best educational efforts, and I don't think that will be universal, but even with good educational efforts, I think there will probably be some significant portion of the population that misinterprets this, and it will cause real personal stress, family stress.

I recognize the increased ability to pick up cancer, and that's the overriding concern, but I think you need to have a more developed plan in place to deal with that.

And my final comment is in looking at the numbers, when we see a relatively small decrease in specificity, but that's a small decrease on a very larger number of patients, and so you're talking about a large number of women.

CHAIRMAN WILSON: Dr. Beavis? Go ahead.

DR. KINNEY: Yeah, may I speak to that briefly?

The decrease in specificity is a concern if, in fact, you're going to take people directly to colposcopy. If, in fact, you're talking about not colposcoping people unless they have abnormal cytology, it's much less of an issue.

I absolutely agree that patient and provider education is the single hardest thing that we do, but I don't think it's warranted to deny the population this useful tool because it's going to be difficult to educate them how to use it.

CHAIRMAN WILSON: Dr. Beavis.

DR. BEAVIS: I think that -- and again, this is Dr. Reller's term -- I think it's very plausible that a longitudinal study would show, you know, that the interval could be safely increased, and obviously, even though the guidelines are out there now, there's obviously some hesitation in using them uniformly in different populations.

And you know, the extra data could help with that, but we've heard -- and in terms of the pathogenesis of the disease, the studies that we've been presented are essentially snapshot studies. The virus comes and goes, and just because someone has the

virus now, yeah, they're at a slightly increased risk over their lifetime for developing it, but the risk is relatively slight.

And that's why I don't think that these questions can be addressed in a single time studying. All of the studies pretty much, except for the Portland study, were that type of study, and the baseline at the Portland study, again, was filled with assumptions based on the three year.

You know, that's the difficulty that I have with this, and that the studies were not longitudinal.

CHAIRMAN WILSON: Yeah, Dr. Nolte.

DR. NOLTE: Going back to the Portland question, the FDA made the point about the validity of the statements in terms of the disease state in the patients in the Portland study based on the sort of one time look at three years and then assigning them a disease state at baseline.

I'd like to hear some lighter discussion about the validity of that assumption or the nonvalidity of it. I mean, these two gentlemen here probably have a perspective on that.

DR. COX: Yeah, in several of these studies you have multiple parameters used to determine

whether somebody is referred to colposcopy. Portland, I believe, we could say would be testing in cytology.

Some of the other studies included cervical photography and some didn't include cervical photography. But you know, in all of these studies where there are multiple parameters, obviously the majority of people who are negative on all multiple parameters were not evaluated, but long term follow-up did not show significant disease developed in the people who were multiple negatives.

That is particularly true in the Costa Rica study where follow-up for seven years never found a single individual in 7,500 that were negative on all three parameters that showed up with a high grade disease or cancer.

So I think that, you know, we have reason to believe that the long-term follow-up in these did take away as far as I'm concerned the issue of verification bias as a single point analysis.

Let the real statisticians speak to that.

DR. KOUTSKY: Just a quick clarification. I think what might have been a bit confusing is the estimate at one point in the materials sounded like it was just measured at three years, and at other points it was anything accumulated up through three years and

estimates all of the CIN3s that occurred up through three years.

MR. CANNER: That is correct, and actually I wanted to talk a little bit more about the Portland study because we do have a longitudinal study, and the data are actually, I think -- and the clinicians can address the clinical relevance of this -- in the Panel pack on page 66, Table 23, there's a Kaplan Meier curve from the Portland study. The study was, you know, some women or the women were followed all the way out to ten years, at least some of them, and so we have a good estimate of risk over that time period.

And after two years, the risk or the survival probability or disease free survival probability was 100 percent after two years and .999 after three years. In other words, the risk of disease was zero after two years and one in 1,000 after three years. I'm sorry, in the PAP negative, HPV negative group.

And they also compare that to the PAP negative, HPV positive group. Granted the risks in that group are not large. This is a rare disease, but the relative risks are very significant, and it clearly shows that you can go out two or three years with an almost nonexistent risk of cervical disease

with the negative/negative.

DR. KINNEY: When we write our practice guidelines, the thing that we rely on most is the experience in our own population, or if we don't have that, in populations closest to ours. The study has now been going on for a decade, as was indicated, and up to this point we haven't seen anything to tell us we're wrong.

This is a study of the size that permits us to draw this conclusion based on the study alone. It's a 10,000 personal longitudinal cohort for ten years.

DR. FELIX: Where is that Kaplan-Meier curve again?

MR. CANNER: Page 66. I'm told it's page 86. Maybe I have a different version, but -- page 66, Table 23.

And also to address the issue of how the -- sorry.

(Pause in the proceedings.)

DR. COX: I think when you get a chance to look at that anyway, you'll see that this study, this one large, 20,000 cohort study followed for ten years in the United States is enough to answer the concerns and questions that we have expressed on this panel

today.

DR. KINNEY: And the sample size I mentioned is the sample size of the patients over 30. It is, in fact, a 20,000 person cohort in toto. I was only making reference to those patients who were informative for the indication that's being discussed today.

DR. LORINCZ: I'd like to point out a few other issues related to the Portland study which I think will help the Panel and audience understand this study better, and especially Dr. Beavis who questioned the availability of longitudinal data.

The full extent of the Portland study was not submitted to the FDA because of our rather limited claims. This is the largest natural history, longitudinal prospective study that has ever been done. It started out with 23,000 women in Portland, and it spanned ten years.

And I can give you a few snapshots, and this is all available in a full scientific paper that has been prepared that is not part of this package.

Of the disease, CIN3, that was detected over a period of ten years, and I believe the number was 148, the PAP smear originally identified approximately 30 to 35 percent, and the HPV test, a

single time -- these are a single time baseline performance -- identified 67 percent, and the two together identified 75 percent, or three quarters of all CIN3 that developed in the entire ten year period in this group of women, which I believe is a very impressive demonstration of the long-term protective effects of having an HPV and PAP negative result.

We believe that the use of cervical vaginal lavage for the HPV test at baseline biased against the value of the HPV because it has been demonstrated that simply washing the vagina will not get endocervical cells, which are more likely representative of high grade lesions.

And in fact, if you look at other studies, such as ALS (phonetic), which has not been mentioned, or many of our other studies that use the brush device, the sensitivity was much higher. So, therefore, there's already an impressive detection of long-term disease which we believe with the correct brush device would actually be higher, not lower.

And I think that that study answers a lot of the questions that have been discussed here at the Panel with respect to longitudinal versus cross-sectional data.

We chose three years because we wanted to

convert to a cross-sectional format for the purposes of introducing consistency across all age studies.

DR. BERRY: Dr. Wilson, I wonder if I can ask something about this.

CHAIRMAN WILSON: Go ahead.

DR. BERRY: Sine we are hanging a bit on this table, I want to make sure there is no difference in the ascertainment of CIN3 in the HPV positive as opposed to HPV negative.

I mean if, for example, we were to follow the guidelines that we were just talking about and the positive had annual tests and the negative had every three years or even more, then you would find more obviously in the positive.

Was there an ascertainment difference?

DR. LORINCZ: Does this work? Can you hear me?

The Portland study was a masked, longitudinal, unbiased study. The HPV --

DR. BERRY: But presumably the women knew that they were positive.

DR. LORINCZ: No, they did not.

DR. BERRY: They did not know.

DR. LORINCZ: For HPV they did not know, absolutely not. In fact, to be specific, the HPV, it

was a retrospective prospective study. All women at baseline had HPV testing collected, and these were stored in a refrigerator, minus 70 degrees, and they were all analyzed between last March and last April.

So, in fact, nobody, not the clinicians, not the epidemiologists knew the HPV status.

DR. BERRY: Thank you.

CHAIRMAN WILSON: Dr. Beavis.

DR. BEAVIS: Thank you. I appreciate your clarifying this for me.

Are you saying that essentially over the ten years 138 women developed cancer?

DR. LORINCZ: One hundred and forty-eight of the women were detected to have CIN3.

DR. BEAVIS: Okay.

DR. LORINCZ: Using repeat PAP smears, the average was probably about three. Some of the women had over seven PAP smears during that interval. So there was a wide diversity because Portland was practicing the variations in follow-up, as we have seen.

DR. BEAVIS: All right, but the combination of PAP and HPV detected approximately 75 percent?

DR. LORINCZ: Seventy-five percent. PAP

alone was -- on the first baseline.

DR. COX: Not over time.

DR. LORINCZ: Not over time.

DR. BEAVIS: Well, you see, that's my question. Because 148 women are going to be diagnosed with it over a ten year period. Okay? But at time zero, 75 percent of these 148 women are picked up --

DR. LORINCZ: With PAP and HPV.

DR. BEAVIS: -- by a combination of --

DR. LORINCZ: Yes.

DR. BEAVIS: -- PAP and HPV.

DR. LORINCZ: Approximately 35 percent by the single PAP

DR. COX: But not at time zero.

DR. LORINCZ: At time zero, that's correct, because the --

DR. BEAVIS: So my question is: for the women who were going to be developing it at year eight, but who are, you know, HPV positive at time zero, what would have happened to them in those eight years?

DR. LORINCZ: They got repeat PAPs, and there was no disease detected on the particular time point. Let's say at year eight, but --

DR. BEAVIS: Wait a minute. We're saying

that we're not going to be doing anything more than additional PAPs following a positive HPV. How would this HPV testing impact what the physician and the women are doing?

DR. LORINCZ: Because it's done more frequently. If the PAP has a certain sensitivity limitation, every time it's performed you miss 40 to 50 percent of the disease. The way you get to a cumulative sensitivity of 99 percent is by repeating it multiple times, let's say, five or six times.

If you can determine the appropriate risk group on which to do more frequent versus less frequent PAPs, you end up with a higher overall sensitivity for all the groups.

And what we're saying is that current guidelines already permit PAP smears up to every three years, and we're simply stating that if the risk to the woman is known with respect to an HPV positive, it is suggested that she be tested more frequently with the PAP to increase the probability that the disease we suspect is there will be detected as opposed to her being a loss to follow-up who develops a malignancy.

DR. BEAVIS: There's 148 women who developed cancer in that period. What percentage of them had a positive PAP smear at some point during

that period?

DR. LORINCZ: Of the 148 women who developed? All of them because the way they were found was by repeat PAP.

This also answers Dr. Noller's question. In the Portland study, the women with disease over the ten year period were only found by the PAP smear. They were cumulatively found by doing multiple repeat PAPs, and when there were a sufficient number of abnormalities, maybe LSIL, HSIL, whatever it was, they were referred to colposcopy, and then the disease was detected.

So all of them were detected by PAP. What I'm saying is that only about 35 percent of them were detected as positive at the baseline PAP, and the rest of them required multiple repeat PAPs to be detected.

CHAIRMAN WILSON: Dr. Gutman. Your mic is not on.

DR. GUTMAN: I don't mean to be a spoil sport here, but we're really moving into information that has not been reviewed by the FDA. We actually looked at this study fair and square as a cross-sectional study, not as a longitudinal study, and it really isn't customary to move into a discussion of new areas in the course of the panel.

So as rich and interested as I actually think this is, I actually think we've strayed a little too far.

DR. BEAVIS: I'm sorry.

CHAIRMAN WILSON: But may we talk about the three years that you did review?

DR. KINNEY: Okay. The clinical utility of this is that in the three years following the onset of the study the negative predictive value for a negative HPV and a negative cytology was asymptotic to 100 percent. That's the basis for feeling that it's acceptable from a clinical perspective to contemplate two or three year screening in women who are double negative. That's the utility from our standpoint.

The study doesn't exit in a vacuum. One of the members of the panel did ground breaking work about this that I'm sure she'd be willing to tell you about, and there are four other studies that were on one of the slides that we talked about also.

Do you want to help me here Laura? No? Okay.

DR. COX: The other thing that I'd like to state is that actually the algorithm we proposed was to do a PAP and an HPV test in a random hear in that basis, and multiple studies, we can talk about these

as well.

It's shown that people with transient HPV that are evaluated in the studies from the first time of detection, about 70 percent of them would become HPV negative by the year, and these are individuals that are not at risk.

I think we need to take that into account and realize that we're not going to be using this as an immediate evaluation scenario, but one which gives us information in the future.

Those people are still positive for the year. Then they are at risk that warrants colposcopy, at least in my professional estimation.

And the early detection is the key to the outcomes that we get. We talk about people being in the Kaiser system, and they'll come in year after year, and it's free for them to get it, but many people are transient themselves and move around and may not get constant care.

I don't believe that missing some CIN3s will always go without consequence, that some people do get cervical cancer in this country who have been screened adequately. There are about 3,000 cases, well, about 30 percent of 12,800 cases in the United States that have had cervical screening on what could

be considered to be an adequate, if not perfect, screening schedule.

So I think we need to keep these things in mind when we talk about all of these issues.

DR. KINNEY: Pursuant to that same question, Dr. Noller had asked me earlier about isn't the decreased detection simply high grade disease that would go away on its own, and the incidence of invasive cancer after a negative smear suggests that that's not true, that that 30 percent both in our data and in the SEER information suggests that there are people who have negative PAPs who have CIN3 that go on to cancer.

CHAIRMAN WILSON: Okay. Other questions from the Panel regarding this question? Comments?

DR. KOUTSKY: I have a question.

CHAIRMAN WILSON: Yes. Could FDA put the first question back up?

Go ahead, Dr. Koutsky.

DR. KOUTSKY: In the U.S. a fair percentage of women who have abnormal PAPs don't follow recommended follow-up because I think it's -- at least it's my understanding that particularly with ASCUS, it's unclear. The clinicians don't want to say, "You have cancer," and so they minimize it and

women are left with this feeling of they're not sure what they're supposed to do with ASCUS.

My question around HPV is: has Digene done any work to look at whether the messages that are given with the positive versus negative HPV test result in a better response to recommended follow-up even just among the data they have with women with ASCUS and HPV testing where it's positive or negative?

Is there any -- a big problem in the U.S. is this follow-up. I think their best studies suggest only somewhere between 30 and 70 percent of women who are recommended for follow-up, colpo. follow-up or a repeat PAP, actually adhere.

DR. COX: I believe there isn't a lot of data on that. I'm not sure you haven't looked at it yourself in your area, but certainly in the ALTS data from center to center there wasn't, I believe, a statistically significant difference in follow-up between those that were HPV positive and those that were HPV negative.

One of the interesting things about the ALTS data is that the women coming in ASCUS HPV positive had much more detection of CIN3 than the women going into premier colposcopy who did not have HPV status known, and the only thing that we did

surmise from that was that the clinicians were more likely to be observant of the cervix and consider it possibly having disease and be more careful about where they did their biopsy points and where there's a significant difference between that and the colposcopy.

I don't have any other data than that.

DR. KILLACKEY: Dr. Koutsky, I don't think we can equate an ASCUS PAP smear with the same thing as knowing that you were HPV high risk positive. An ASCUS PAP smear, when we all would get them back and give them to our patients, we really truly didn't know what the significance of that would be, and most of the time it isn't significant.

Positive HPV screen in a 30 year old woman means something. It means she has, as the data have shown, a predilection to develop cervical neoplasia. So now we do have a piece of information that does confer a significant risk.

ASCUS doesn't do that. ASCUS says, as reported back in the country, and the two and a half, three million PAP smears, we really had no idea what to do.

DR. FELIX: Well, I'm not sure you can say that because the rate of abnormalities in an ASCUS

population is very almost identical to the rate of abnormality in an HPV positive population, if not higher. The rate of positive high grade disease in the ASCUS population is ten percent.

So I'm not sure that you can say that. I mean, there is a large number of women who have nothing, 80 percent, but still the rate of positivity is very significant.

DR. LORINCZ: Dr. Felix.

CHAIRMAN WILSON: Excuse me. You haven't been recognized.

We want to take a very short break here because we're having some technical problems with the sound system. So we're just going to stop for about five minutes. If you want to stretch your legs, that's okay, but don't go too far and try to be back within five minutes.

(Whereupon, the foregoing matter went off the record at 2:17 p.m. and went back on the record at 2:26 p.m.)

CHAIRMAN WILSON: We haven't found out what the source of the interference is. One possible thing is someone may have something plugged in somewhere, into one of the electrical circuits in the wall. So if you have something like that, please

disconnect it. It could be something such as a battery charger or something like that.

Because some data were mentioned by the sponsor that have not been part of the review, FDA would like a chance to comment on that data. I'm going to turn it over at this point to Dr. Gutman.

DR. GUTMAN: As beguiling as that data is, we really were a little over the edge. It really was moving into an area of information that could be submitted and could be evaluated, but has not, and we really need to ground it in the data that's at hand.

So I'm going to ask Marina if she will do that by grounding it in the data that is at hand.

DR. KONDRATOVICH: So this is the data for important study, and I would like to bring your attention that the amount 28 subjects are HPV not detected, 11 woman, and detected 70. So this 11 woman can have the full security that they don't need to do PAP test during three years.

And so what it can -- so what is your opinion about this?

DR. BERRY: Marina, these are PAP tests at baseline?

DR. KONDRATOVICH: This is the problem because --

DR. GUTMAN: Yes.

DR. KONDRATOVICH: Yes, this is PAP test at baseline.

DR. BERRY: And so those 11 were actually those that were found in subsequent PAP smears.

DR. KONDRATOVICH: Yes, but they have HPV negative. So if they decided not to detect it during this three years by PAP test, so this woman will be missed, and this is about 40 percent from this woman.

CHAIRMAN WILSON: Okay. So does anyone on the Panel have any questions about that?

DR. JANOSKY: Could you just put up the summary statistics also for the Portland study?

DR. KONDRATOVICH: But this is the summary (unintelligible) time point measurement. This is at baseline. So this study has some kind of an error because this is on baseline.

DR. BERRY: Could you go back to the previous one?

The 11 should be compared with the 9,053 because both of those had the same characteristic. One got disease and the one didn't. So the predictive value is 11 over 9,000 or something.

CHAIRMAN WILSON: Okay. Any further questions or comments regarding those data?

DR. KONDRATOVICH: So right now we don't get the information about we can extend the period for three years. So the data which are presented in that kind of table because the HPV doesn't appear to have any inference for extending of period of between PAP tests. So we don't know exactly what is the probability for this event.

CHAIRMAN WILSON: Okay. Thank you very much.

Dr. Gutman, do you have any further comments?

DR. GUTMAN: Not at this time.

CHAIRMAN WILSON: Okay. At this point we need to wrap up the discussion on the first question. Are there any issues that anyone on the Panel would like to bring up on the first question before we move on to the next?

DR. NOLTE: There was some discussion at some point about doing a simplified data analysis including only those issues that were cytologically negative and looking at that. Was that done?

DR. KONDRATOVICH: In my own presentation I also speak separately about the PAP negative, and especially you can pay attention to my last slide about the number for what it takes to get one true

positive. This is particular for the PAP negative, the cytology (unintelligible).

DR. BERRY: Also, the table that I put up was for a PAP negative, and by the way, that referred to CIN3.

CHAIRMAN WILSON: Okay. Any further comments about the first question?

Dr. Gutman, do you think you have enough information at this point?

Okay. If we could have the FDA put up the second question, please.

MR. SIMMS: Question No. 2 we would like the Panel to comment on: is Digene's criteria of decreasing the false negative rate lower than 25 percent and not decreasing specificity, in other words, the true negative rate, by more than ten percent acceptable to measure the benefit of adding high risk HPV DNA testing to the normal PAP smear?

CHAIRMAN WILSON: Dr. Berry.

DR. BERRY: I answered this for myself previously. My answer was no, that you need to address the implications of the test, what the consequences are, and that sensitivity and specificity, while relevant, are not the only things nor the important things to address.

CHAIRMAN WILSON: Are there any other comments or questions from the Panel?

Dr. Koutsky.

DR. KOUTSKY: To some extent I think basically all you can address is the sensitivity and specificity because the positive and negative predictive values will vary so much by different populations depending on the prevalence of the disease.

So I'm not sure if there were different criteria, what would you propose would be better criteria?

DR. BERRY: Well, I do think positive predictive value and negative predictive value is the appropriate thing. You know, what is the implication as you go along the sequence from here we start, here we get a PAP and then we get an HPV, and addressing the consequences of the positive and the negative results of the various tests.

So, I mean, if the prevalences of the disease is very low, then sensitivity, I mean, even if we get sensitivity of 100 percent, it doesn't matter. What matters is what is the impact on health policy. What is the impact on an individual woman?

And sensitivity and specificity don't

address that because they don't address the absolute risk or the absolute benefit. What they address is a relative risk and relative benefit.

CHAIRMAN WILSON: Dr. Felix.

DR. FELIX: Yeah, and again, even though the concept is correct, and I think we discussed this slightly in a side bar, I believe that the clinical aspects to that, to sensitivity add, even though it does not add to the positive predictive value in that positive predictive value does not take into account future risk of disease in women who are HPV positive and currently disease undetectable, but who will develop the disease.

So it mirrors a little bit of what Dr. Cox said, that it has to be treated carefully. How do you treat a false positive test?

So I'm not 100 percent in agreement that the positive predictive value is the only thing we should consider because it is greatly affected by the fact that you're counting them as false positives when, in fact, they might not be false positive.

And if we are going to look at thresholds like sensitivity and specificity, I think that clinically speaking a 25 percent improvement in sensitivity is a reasonable threshold. I think that

it is certainly a -- I couldn't come up with a better one looking at the data myself.

CHAIRMAN WILSON: Dr. Berry.

DR. BERRY: I could come up with a better one. The better one is zero. The standard thing to do in medical research is to ask the question: does something matter? Does the treatment affect the disease?

And here we're asking: is the conclusion affected by the test?

If sensitivity is statistically significant, then you say, "Okay. We know it does something. Now let's get on with the question of what does it do and what are the consequences."

So if it were me, I would say, "Let's test the hypothesis that sensitivity is better with HPV than it is without HPV, and if it is highly statistically significant, let's get on with the real question."

CHAIRMAN WILSON: Yes, Dr. Birdsong.

DR. BIRDSONG: In regard to the 25 percent increase or decrease in false negative rate, I already spoke my mind about the false positive issue, but this is still, after all, proposed as an adjunct to improve cancer screening, and I think the most important

aspect of the screening test is actually the negative predictive value, again, affected by prevalence of the disease in the population, but in all of the studies the negative predictive value is so good with this that I think that 25 percent is reasonable.

As for the ten percent decrease in the specificity, you know, I have concerns about that, but I've already spoken to that.

CHAIRMAN WILSON: Other comments?

DR. NOLTE: The relative risk for developing cancer in the double negative group versus the group that has a positive HPV test is fairly well established, and that seems to me, I mean, we're talking about -- that hasn't come up as a parameter here, and I wonder why it hasn't.

And using that as validation for the extended, you know, application here, it seems like it's a reasonable one to me. I just wonder why that hasn't been part of our discussion today.

CHAIRMAN WILSON: Dr. Berry.

DR. BERRY: We did look at a table that addressed that, but it was suggested that that that hadn't been presented to the FDA, and so we couldn't do it.

DR. NOLTE: Well, the data was in the

packet.

DR. GUTMAN: The data in the packet is kosher. What I was concerned about was when we started introducing other longitudinal data. So what you see is what you got. Either we or the sponsor missed it, and if you'd like to discuss it, you're certainly free to do that.

DR. BERRY: The bottom line is after five years there were seven per 1,000 in the HPV negative, and there were 47 per 1,000 in the HPV positive. those are PAP negative.

So that's a rather dramatic difference.

DR. NOLTE: That for me is the most meaningful parameter, not positive predictive value, not sensitivity, not specificity. That is what argues strongest with me.

DR. BERRY: I agree that's very relevant.

CHAIRMAN WILSON: Dr. Ng.

DR. NG: Well, I was hoping to address Rick's question by looking at the table on the number of false positives versus true positives if you were introducing HPV testing. It means depending on the prevalence that ratio was anywhere from ten to one up to 40 to one, up to if you live in China in a high prevalence setting 160 to one.

So you know, if you were providing this test and yield a positive HPV result with a negative PAP, how are you going to counsel that woman at that point in time? And I think those are the numbers.

DR. BERRY: Just one quick comment on that. One hundred and sixty to one was one patient to 159, and the average was 15, I think, over the entire set, which is a relevant consideration comparing those two.

CHAIRMAN WILSON: Dr. Weinstein.

DR. WEINSTEIN: Well, that cuts right to the core of my question and degree of comfort or discomfort, namely, how many false positives are you willing to accept for each true positive?

I don't know the answer to that, but that's the dilemma that's going around in my head.

DR. FELIX: I agree. Exactly what does that false positive means is something that adds to the complication, at least in my mind, because there may not be false positives, but it's undetectable disease, and I do colposcopy. There's times when I'll do colposcopy in three biopsies on a patient, and that patient has disease. It's just that we missed it on those.

CHAIRMAN WILSON: Dr. Beavis.

DR. BEAVIS: And part of the complication with this whole incident of false positive or not is we have to realize that what the test is detecting is the presence or absence of virus at that time, not the presence or absence of cancer.

And that's why we can come to different conclusions as to whether or not it's a false positive or not depending on whether we're looking for virus or whether we're looking for cancer and using the test as a surrogate marker for cancer.

CHAIRMAN WILSON: Dr. Noller.

DR. NOLLER: This is purely semantic, but none of this has to do with cancer. We're looking at cancer precursors. Let's just remember that. These are not cases of cancer we're detecting, but interepithelial neoplasia, some of which if left untreated might develop cancer. But this is not cancer.

CHAIRMAN WILSON: All right. Are there any further comments or questions about the second question?

(No response.)

CHAIRMAN WILSON: Okay. If we could have the FDA put up the third question, please.

MR. SIMMS: The third question we would

like the Panel input on: if the Panel does find the new indication for use as a general population screening test acceptable, how might the device be labeled and what recommendations should be made for its use given the different populations and conditions used to derive the data and the non-poolable nature of the data?

CHAIRMAN WILSON: Dr. Noller?

DR. NOLLER: Just one comment. We received a huge volume of paper and different copies of things. In some places the indication suggested that hybrid capture II was to be used for this. Others said a high risk panel of hybrid capture II.

I just want to be clear we're looking at only the high risk panel, right, not the low risk panel?

DR. GUTMAN: That's correct.

DR. NOLLER: Though it wasn't specifically stated that way in most of the stuff I saw.

DR. GUTMAN: Yes, that's correct.

DR. NOLLER: Thank you.

CHAIRMAN WILSON: Dr. Berry.

DR. BERRY: If I put that sentence in my Microsoft Word document, it would underline it saying the sentence is too long.

(Laughter.)

DR. BERRY: It's too long for me. If we separate out the given part, what comes after given to me is kind of a red herring. As I suggested, we have to make recommendations for -- we have to do the synthesis, and so you can't say that studies are not poolable and the eventual decision had to pool them.

But if we can separate that out and just focus on the first phrase, I think that would help, and I don't have much to contribute to that except that I think it's absolutely critical.

CHAIRMAN WILSON: Further comment?

I think the FDA is looking for some help here about if there's any concerns that the Panel members have about what sort of weighting or recommendations could be used to mitigate those concerns.

DR. BERRY: Well, Dr. Wilson, this is related to the stuff that we talked about earlier about prolonging the interval of screening, about maybe an earlier or a more frequent PAP test about colposcopy.

I assume from what the sponsor has suggested that the sponsor would say, "Do not do colposcopy if you're PAP negative, HPV positive," and

so they are presumably recommending that that recommendation be put in the labeling.

I don't know whether that's a correct thing to do or not, but it's a can of worms

CHAIRMAN WILSON: Other comments? Dr. Nolte.

DR. NOLTE: I've heard two opposing views, one from the sponsor and one from the FDA on the poolability of the data. I heard one set of statistical consultants say that the data was poolable, and I heard the FDA say it was absolutely not poolable.

Not being a statistician, I don't know how to respond or how to process that information.

DR. BERRY: Just to correct my -- my interpretation is that I'm the only one in the room that said it should be pooled. The sponsor said it's not poolable, and the FDA said it's not poolable.

DR. NOLTE: Oh, okay. I thought -- okay. That's all right.

DR. FELIX: But I think that Dr. Koutsky's comment that, in fact, our population in the United States is not poolable either is very pertinent. In other words, you don't screen an upper middle class neighborhood the same way that you screen an urban